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Werkwijze ter bereiding van nieuwe oxytocisch werkzame verbindingen en preparaten.

Aanvrage No. 164737 Ned., ingediend 17 October 1951, 24 uur; openbaar gemaakt 16 November 1953.

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Bij de toepassing van uterus-contraherende middelen in de gynaecologie gebruikt men tot nu toe vrijwel uitsluitend het oxytocisch-actieve hormoon van de hypophyse-achterkwab of moederkoorn-alkaloïden, bij voorkeur het in water oplosbare ergometrine. Tot dusver is nog niet veel bekend over synthetische oxytocica. Nochtans bestaat daaraan behoefte, mede door de toenemende schaarste en oplopende prijs van het moederkoorn.

Aanvraagster heeft nu gevonden, dat 3-(alkylpiperidyl-(N)-methyl)-indolen een sterk oxytocische werking hebben. Men kan deze verbindingen afgeleid denken van 3-(piperidyl-(N)-methyl)-indol door in de piperidylgroep één of meer waterstofatomen te vervangen door alkylgroepen.

In de octrooiaanvrage 157.342 Ned.[1]) ten name van aanvraagster is de sterk oxytocische werking beschreven van 3-(piperidyl-(N)-methyl)-indol. In tegenstelling met deze verbinding, zijn de onderhavige gealkyleerde verbindingen nieuw. Ze hebben een oxytocische werking, welke die van het 3-(piperidyl-(N)-methyl)-indol vaak evenaart en in een aantal gevallen overtreft.

Deze 3-(alkylpiperidyl-(N)-methyl)-indolen kan men op verschillende wijzen bereiden. Men kan bijvoorbeeld het betreffende alkylpiperidine in reactie brengen met indol en formaldehyd; men kan ook aequimoleculaire hoeveelheden dimethylaminomethylindol resp. diaethylaminomethylindol met het desbetreffende alkylpiperidine verwarmen. Deze bereidingswijzen zijn voor analoge verbindingen beschreven door Kühn en Stein (Ber. 70, 567 (1937); men vergelijke ook het Duitse Octrooischrift 673.949) resp. Howe, Zambito, Snijder en Tishler, J. Am. Chem. Soc. 67, 38 (1945).

De bereiding van enkele verbindingen uit deze nieuwe reeks van 3-(alkylpiperidyl-(N)-methyl)-indolen zal hieronder nader worden toegelicht.

Voorbeeld I.

3-(2'-methylpiperidyl-(N)-methyl)-indol.

Bij 80 g α-pipecoline wordt onder ijskoeling 81 cm³ ijsazijn gedruppeld. Na toevoegen van

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74 cm³ formaline en 97 g indol wordt het mengsel goed doorgeroerd. Onder vrij sterke warmteontwikkeling vormt zich een zwak gele olie. Na 4 uren staan bij kamertemperatuur wordt het reactiemengsel met 1 liter water verdund en vervolgens met ammonia alkalisch gemaakt. De zich afscheidende gum kristalliseert snel.

Het ruwe reactieproduct wordt afgezogen, met water gewassen en aan de lucht gedroogd. Na herkristalliseren uit 400 cm³ aceton wordt 142 g van de zuivere verbinding van smpt 171—173° C (ontl.) verkregen.

Voorbeeld II.

3-(3'-methylpiperidyl-(N)-methyl)-indol.

Met 30 g β-pipecoline.HCl, 30 g natriumacetaat.3 aq., 9 cm³ ijsazijn, 20,2 cm³ formaline en 26,6 g indol wordt, als men verder werkt volgens voorbeeld I, 33,6 g zuiver reactieproduct verkregen, dat na herkristalliseren uit aceton, een smpt van 147—149° C vertoont.

Voorbeeld III.

3-(4'-methylpiperidyl-(N)-methyl)-indol.

Met γ-pipecoline.HCl als uitgangsproduct en met overigens dezelfde hoeveelheden reactiecomponenten als in voorbeeld II wordt 44 g van het gewenste product verkregen, dat na herkristalliseren uit ligroïne-aether, een smpt vertoont van 108—109° C.

Voorbeeld IV.

3-(2'.4'-dimethylpiperidyl-(N)-methyl)-indol.

60 g 2.4-dimethylpiperidine.HCl (smpt 185—188° C) wordt gemengd met 55 g gepoederd natriumacetaat.3 aq., 16 cm³ ijsazijn en 37 cm³ formaline, waarna 47 g indol wordt toegevoegd. Na hernieuwd doorroeren wordt het mengsel vrij snel warm. Na 30 minuten roeren wordt 80 cm³ methanol verdund en het mengsel nog korte tijd verwarmd. Bij staan scheidt zich het reactieproduct kristallijn af; het geheel wordt met water

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A Method for the Preparation of New Oxytocically Active Compounds and Preparations.

Dutch Patent Application No. 164737, filed October 17, 1951, 12:00 p.m.; published November 16, 1953.

Up to now, application of uterus-contracting preparations in gynecology has almost exclusively involved the use of the oxytocically active hormone of the posterior hypophysial lobe, or ergot alkaloids, preferably water-soluble ergometrine. To date, not much is known about synthetic oxytocin preparations. Nevertheless, there is a need for such preparations, partially due to the increasing scarcity and rising price of ergot.

The Applicant has now determined that 3-(alkylpiperidinomethyl)indoles have a strongly oxytocic action. These compounds can be considered to be derived from 3-(piperidinomethyl)indole by replacement of one or more hydrogen atoms in the piperidyl group with alkyl groups.

In Dutch Patent Application 157,342,[1] in the name of the Applicant, the strongly oxytocic action of 3-(piperidinomethyl)indole is described. In contrast to this compound, the present alkylated compounds are new. They have an oxytocic effect which is equal to, and in a number of cases, superior to that of 3-(piperidinomethyl)indole.

These 3-(alkylpiperidinomethyl)indoles may be prepared in a variety of ways. For example, the alkylpiperidine in question may be reacted with indole and formaldehyde; one can also heat equimolar amounts of dimethylaminomethylindole or diethylaminomethylindole with the corresponding alkylpiperidine. These preparation methods have been described for similar compounds by Kühn and Stein (Ber. 70, 567 (1937); also see German Patent Gazette 673.949) and Howe, Zambito, Snijder, and Tishler, J. Am. Chem. Soc. 67, 38 (1945).

The preparation of a few compounds from this new series of 3-(alkylpiperidinomethyl)indoles will be described in further detail below.

Example I

3-(2'-Methylpiperidinomethyl)indole

81 cm³ of glacial acetic acid is added dropwise to 80 g of α-pipecoline under cooling with ice. Following the addition of 74 cm³ of formalin and 97 g of indole, the mixture is thoroughly

agitated. A considerable amount of heat is produced, and a pale yellow oil forms. After having been left standing for 4 hours at room temperature, the reaction mixture is diluted with 1 l of water and then alkalinized with ammonia. The precipitating gum crystallizes rapidly.

The crude reaction product is suctioned off, washed with water, and air-dried. After recrystallization from 400 cm³ of acetone, 142 g of the purified compound is obtained with a melting point of 171-173°C (decomposition).

Example II

3-(3'-Methylpiperidinomethyl)indole

Using 30 g of ß-pipecoline HCl, 30 g of sodium acetate 3 aq., 9 cm³ of glacial acetic acid, 20.2 cm³ of formalin, and 26.6 g of indole, and proceeding otherwise as described in Example I, 33.6 g of purified reaction product is obtained with a melting point of 147-149°C after recrystallization from acetone.

Example III

3-(4'-Methylpiperidinomethyl)indole

Using γ-pipecoline HCl as a starting product and otherwise using the same amounts of the reaction components as in Example II, 44 g of the desired product is obtained with a melting point of 108-109°C following recrystallization from ligroin/ether.

Example IV

3-(2',4'-Dimethylpiperidinomethyl)indole

30 g of 2,4-dimethylpiperidine HCl (melting point 185-188°C) is mixed with 55 g of powdered sodium acetate 3 aq., 16 cm³ of glacial acetic acid, and 37 cm³ of formalin, after

1) Published 16 November 1953

which 47 g of indole is added. After again being thoroughly stirred, the mixture becomes warm quite quickly. After stirring for 30 minutes, 80 cm³ of methanol is added, and the mixture is again heated for a short period. When left standing, the reaction product is deposited in crystalline form, and the entire substance is then diluted with water and made ammoniacal, after which the base is extracted by shaking with ether.

A slowly crystallizing syrup is obtained from this. Recrystallization of the substance from ligroin (90-100°C) yields 9 g of purified compound having a melting point of 104-106°C.

Example V

3-(2',6'-Dimethylpiperidinomethyl)indole

Using 2,6-dimethylpiperidine HCl (melting point 288-291°C) as a starting product, and proceeding otherwise with the same amounts of reaction components as described in Example IV, 36 g of purified substance is obtained with a melting point 113-114°C after recrystallization from benzene.

Example VI

3-(2',4',6'-Trimethylpiperidinomethyl)indole

Using 68.5 g of 2,4,6-trimethylpiperidine HCl (melting point 310-314°C), 45 g of sodium acetate 3 aq., 13 cm³ of glacial acetic acid, 30 cm³ of formalin, and 38.5 g of indole, and proceeding otherwise with the same reaction conditions and processing methods as in Examples IV and V, one obtains 40.5 g of this compound with a melting point of 111-112°C following recrystallization from ligroin.

Example VII

3-(2'-Ethylpiperidinomethyl)indole

Using 23 g of 2-ethylpiperidine, 20.4 cm³ of glacial acetic acid, 18.7 cm³ of formalin, and 24.5 g of indole, and proceeding otherwise as in Example I, 30 g of purified reaction product is obtained following recrystallization from alcohol. Melting point 160-161°C.

Example VIII

3-(2'-n-Propylpiperidinomethyl)indole

Again using the method of Example I, one obtains 13 g of purified final product from 25 g of 2-n-propylpiperidine, 19.2 cm³ of glacial acetic acid, 17.6 cm³ of formalin, and 23 g of indole following recrystallization from ligroin. Melting point 97-99°C.

Example IX

3-(4'-Ethylpiperidinomethyl)indole

By the method of Example I, 80 g of 4-ethylpiperidine, 71 cm³ of glacial acetic acid, 65 cm³ of formalin, and 85 g of indole yield 110 g of crude product, from which 82 g of the purified product having a melting point of 121-122°C is

obtained by recrystallization from acetone.

Example X

3-(2'-Methyl-5'-ethylpiperidinomethyl)indole

By the method of Example IV, 80 g of 2-methyl-5-ethylpiperidine HBr (melting point 170-172°C), 52.3 g of sodium acetate 3 aq., 15 cm³ of glacial acetic acid, 35 cm³ of formalin, and 45 g of indole yield 85 g of crude product. By recrystallization from ligroin, 74 g of purified substance is obtained with a melting point of 103-104°C.

The oxytocic action of these compounds, administered in the form of their salts, is compared with that of ergometrine in a rabbit uterus in situ sensitized with estrone. If we take the effect of ergometrine as 1, then the effects of the various methyl compounds, for example, appear to be as follows:

3-(2',4',6'-trimethylpiperidinomethyl)indole has an effect of 0.25;

3-(2',4'-dimethylpiperidinomethyl)indole has an effect of 0.33;

3-(2'-methylpiperidinomethyl)indole has an effect of 0.50;

3-(2'-6'-dimethylpiperidinomethyl)indole has an effect of 0.63.

Generally speaking, it appears that when the piperidyl group has alkyl groups at position 2, and particularly when it has them at positions 2 and 6, the compound has an extremely strong oxytocic action. This applies in particular when the alkyl groups are methyl groups. However, compounds such as 3-(4'-ethylpiperidinomethyl)indole and 3-(2'-methyl-5'-ethylpiperidinomethyl)indole are also effective, although not as strongly as the methyl compounds described above, at least as far as their effect on the uterus in situ is concerned; the latter two compounds, however, have approximately the same powerful effect on the isolated uterus as the methyl compounds mentioned above.

The new compounds according to the invention are preferably administered in the form of their salts, such as hydrochloride or maleate salts. It should be noted that ergometrine is administered chiefly in the form of a maleate and not as a hydrochloride. For example, the compounds or their salts may be taken in tablet form together with fillers commonly used in tablet production, such as lactose, cornstarch, talc, and magnesium stearate. They can also be easily dissolved in water in the form of their salts, making it possible following sterilization to obtain usable preparations for injection, with the use of pyrogen-free water being preferred.

Claims

1. A method for the preparation of oxytocically active compounds, in which 3-(alkylpiperidinomethyl)indoles are prepared by a method which is known for such compounds.

2. The method of Claim 1, in which compounds are prepared which have an alkyl group at least at position 2 in the piperidyl group.

3. The method of either Claim 1 or 2, in which the alkyl group is a methyl group.

4. The method according to one of the above Claims, in which an alkylpiperidine is reacted with indole and formalin.

The method of one of Claims 1 through 3, in which an alkylpiperidine is reacted with a dialkylaminomethylindole.